Engineering the Interface Between Cellular Chassis and Integrated Biological Systems

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1 Abstract

The engineering of biological systems with predictable behavior is a challenging problem. One reason for this difficulty is that engineered biological systems are embedded within complex and variable host cells. To help enable the future engineering of biological systems, we are studying and optimizing the interface between an engineered biological system and its host cell or "chassis". Other engineering disciplines use modularity to make interacting systems interchangeable and to insulate one system from another. Engineered biological systems are more likely to work as predicted if system function is decoupled from the state of the host cell. Also, specifying and standardizing the interfaces between a system and the chassis will allow systems to be engineered independent of chassis and allow systems to be interchanged between different chassis. To this end, we are building dedicated transcription and translation systems, independent from the equivalent host cell systems. In parallel, we are developing test systems and metrics to measure the interactions between an engineered system and its chassis. Lastly, we are exploring methods to "port" a simple engineered system from a prokaryotic to a eukaryotic organism so that the system can function in both organisms.

2 Introduction - engineering biological systems: past and future

It is becoming possible to engineer simple multi-component systems in living organisms based on transcriptional logic [Elowitz 2000; Gardner 2000; Hooshangi 2005]. While today's engineered biological systems hint at a future ability to design and build complex systems with many components, the engineering of functional systems is still difficult and time consuming, more akin to art than engineering. Furthermore, current engineered systems are highly sensitive to host physiology and environmental conditions [Elowitz 2002; Rosenfeld 2005].

The future engineering of biological systems will be greatly facilitated by adopting some of the concepts that have proved useful in other engineering disciplines. Central among these concepts are the ideas of standardization of components (e.g. http://parts.mit.edu) and abstraction, which lead to the concept of modularity. Currently, engineered biological systems are dependent on natural host cells. Constructing modular systems is made difficult by the complexity of the host cells and the numerous interactions between the host cell and the engineered system. The development of engineered systems would be accelerated if system engineers did not have to consider all the details of the host cell. Modularization can be achieved by making the interactions between the engineered system and the host cell simpler and standardized.

3 The chassis/system interface

Engineered biological systems typically rely on the host cell for the processes of replication, transcription, translation and degradation and the requisite energy and materials to power those processes. In this way, the cell acts as a power supply and chassis that insulates and drives the system [Knight, T.F. Jr., personal communication].

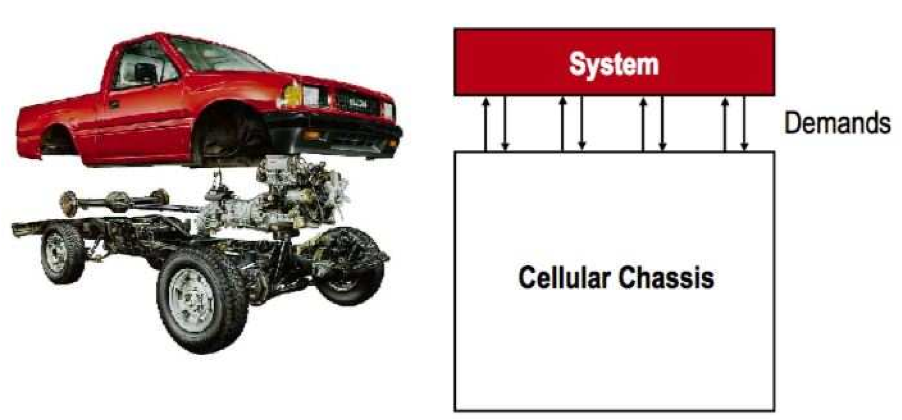
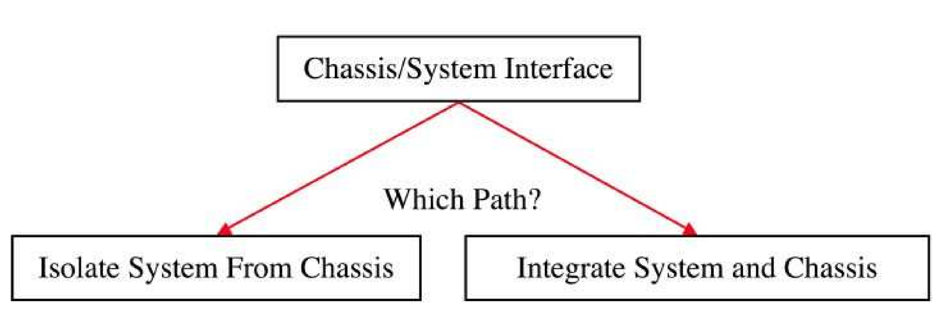


Figure 1 - Just as the power supply and chassis of an automobile support the driver and the accessory systems, so the cell supports an engineered biological system.

Useful characteristics of a chassis/system interface

- Perturbations in the environment or the chassis should not be transmitted to the system.
- Changes in the function of the system should not affect the function of the chassis.
- The system and the chassis should share different resource pools.
- A standard chassis/system interface will allow interchangeability of systems and chassis.
- The chassis/system interface should be simple to improve predictability of system function.

4 Two approaches to interface design



Isolate System From Chassis	Integrate System and Chassis
Improved portability and modularity of systems	Systems are neither portable nor modular
Possibly inefficient use of chassis resources	Resource use may be more efficient as it is shared with the chassis
Can largely ignore chassis systems	Cannot ignore chassis systems
May not be possible to isolate system from worst sources of chassis variation	May require re-engineering of chassis systems if performance is not adequate

- The two approaches are not mutually exclusive and are in fact complementary.
- The systems that must be quantified in one approach must be built in the other.
- The integrated approach provides benchmark data on what isolated system components must be capable of.

5 Dedicated systems

- Transcription and translation systems that are dedicated to an engineered system can be used to separate the demands of the system and the chassis.
- Dedicated systems can be used as a standard interface between systems and chassis.

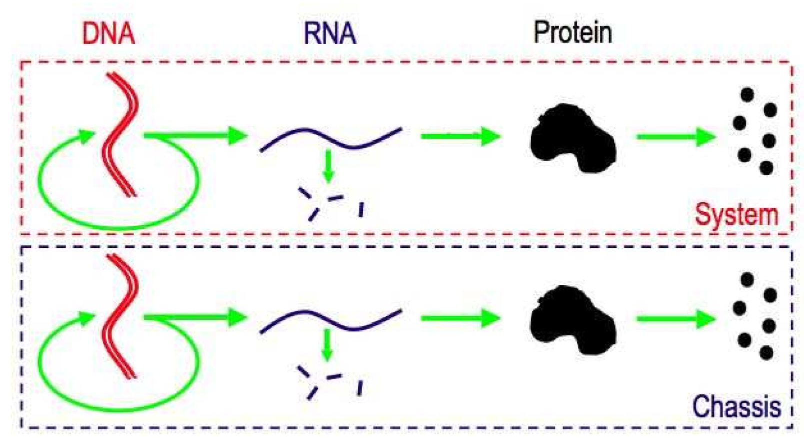


Figure 2 - Dedicated systems can be used to separate the gene expression process of an engineered system from that of the cellular chassis.

6 A biological virtual machine

- A software virtual machine allows an application to function as expected regardless of the computer architecture running the virtual machine.
- A biological virtual machine allows an engineered biological system to function as expected regardless of the cellular chassis running the virtual machine.

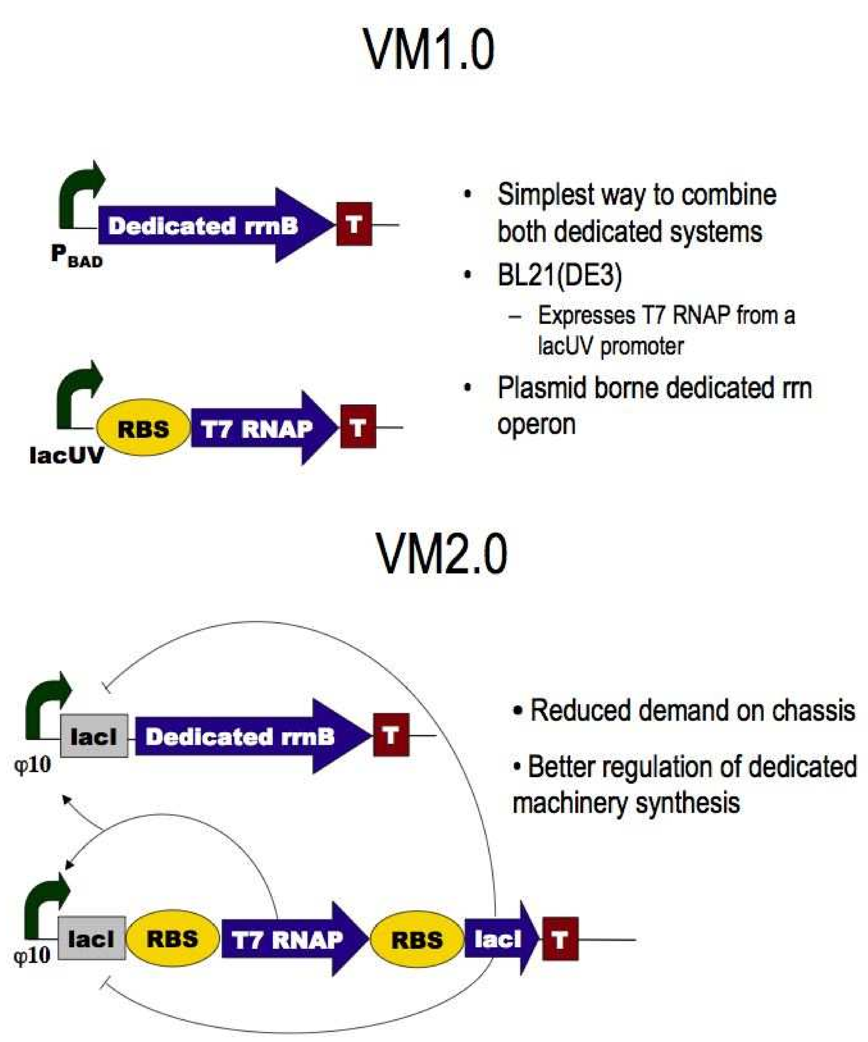


Figure 3 - Two early versions of a virtual machine.

7 VM1.0 preliminary results

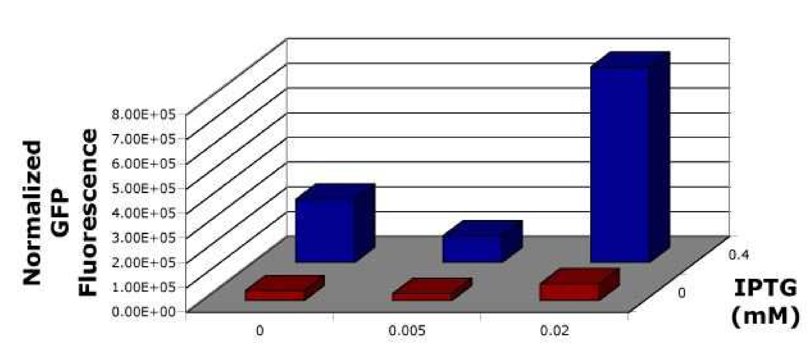


Figure 4 - High levels of GFP expression are only seen when the reporter gene is transcribed (T7 polymerase is induced by IPTG) and when GFP mRNA are translated (dedicated ribosomes are induced by arabinose).

8 Measuring chassis response

- Can we measure the demand a system places on a chassis and the response of the chassis?
- How does a cellular chassis respond to an applied demand for machinery, materials or energy?
- Can this demand be specified quantitatively?
- Can we predict *a priori* what the demand placed by a system on the cellular chassis is?

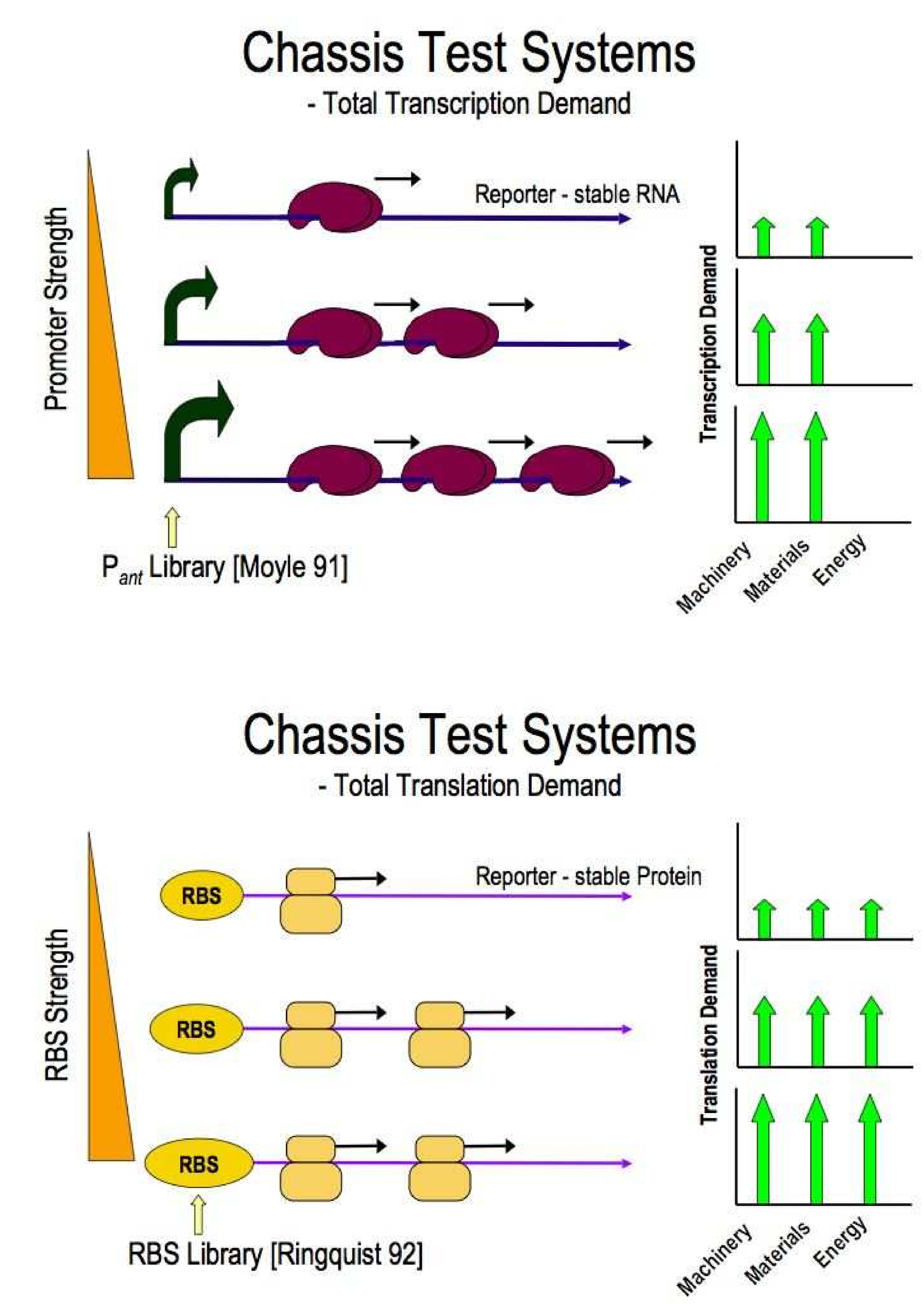
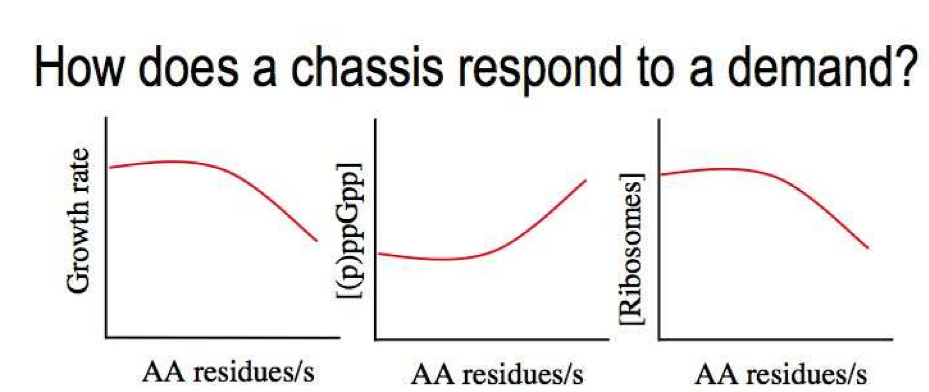
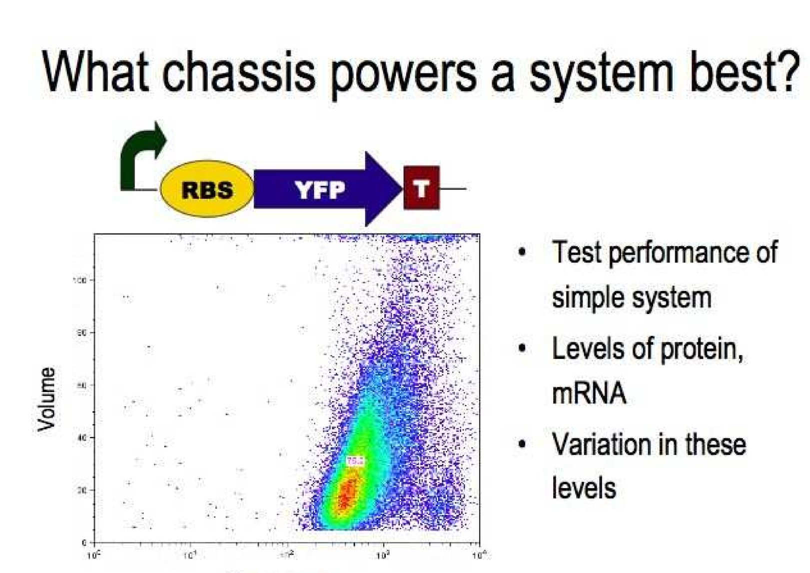


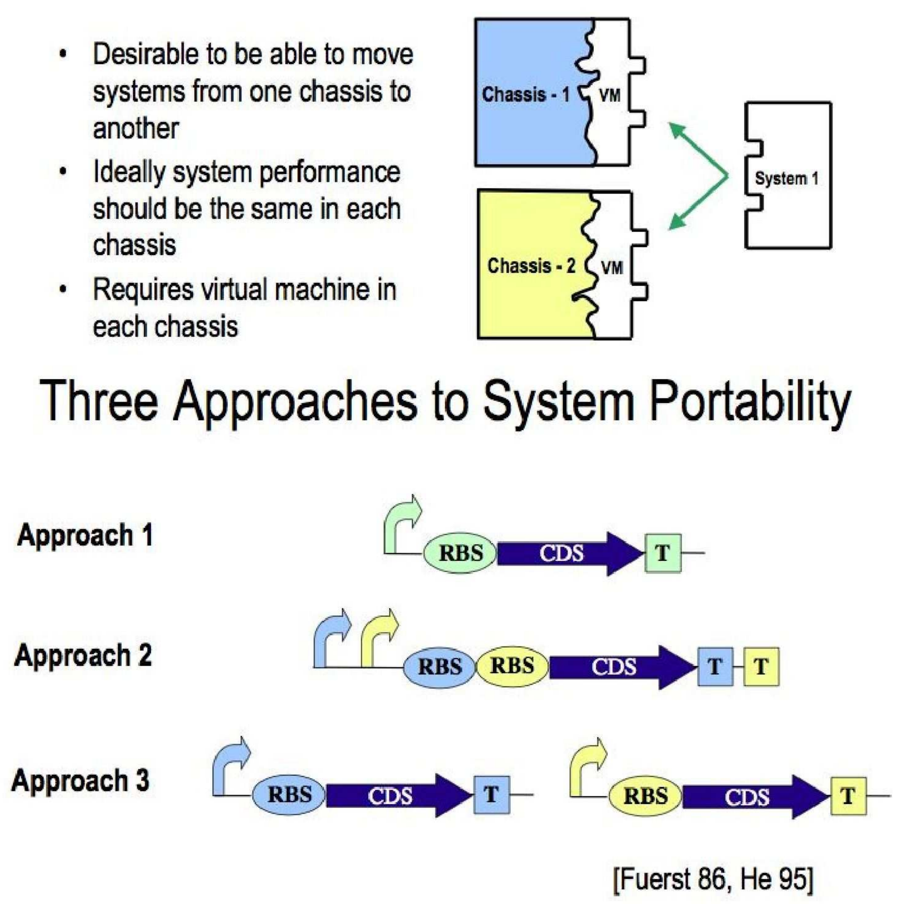
Figure 5 - Methods to place a demand that can be specified on a cellular chassis.



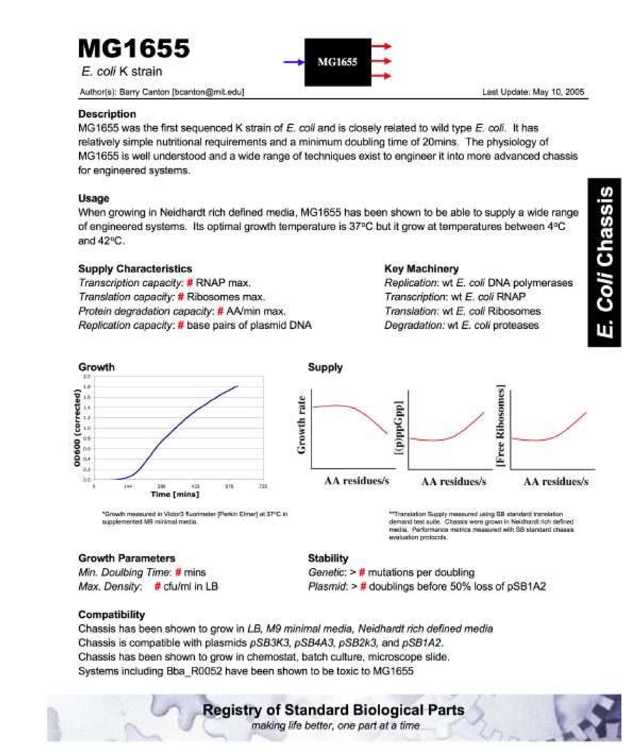
- What demands can be placed on a chassis before system performance is affected?
- Is the transition sharp?
- Rate dependence?

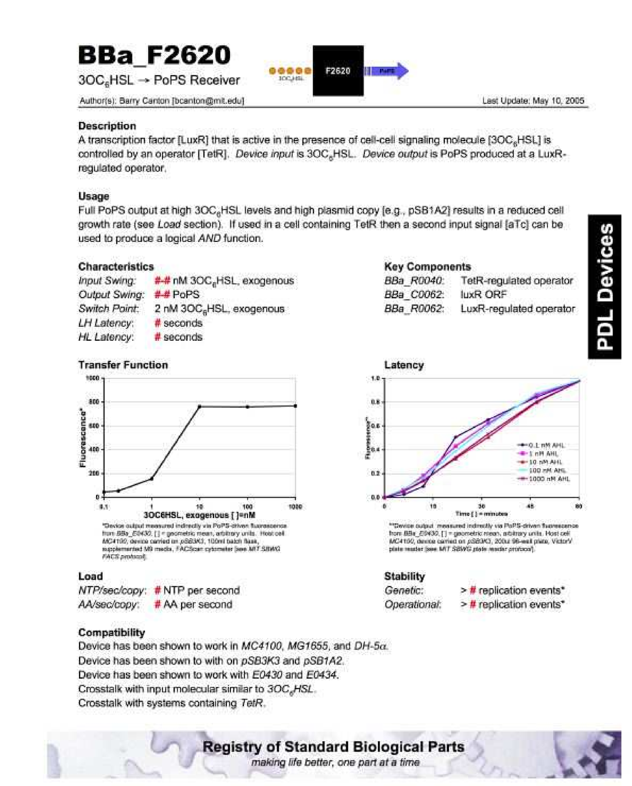


9 System portability



10 Chassis and system data sheets





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